PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
C07D 233/54, A61K 31/415	A1	WO 93/13074
		(43) International Publication Date: 8 July 1993 (08.07.93)

(21) International Application Number: PCT/FI92/00349

(22) International Filing Date: 18 December 1992 (18.12.92)

(30) Priority data:
9127050.4 20 December 1991 (20.12.91) GB

(71) Applicant *(for all designated States except US):* ORION-YHTYMÄ OY [FI/FI]; Orionintie 1, SF-02200 Espoo (FI).

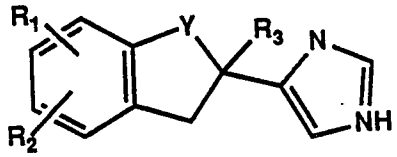
(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* KARJALAINEN, Arto, Johannes [FI/FI]; Myllyojantie 13 H 37, SF-90650 Oulu (FI). VIRTANEN, Raimo, Einari [FI/FI]; Knaapintie 2-4 as. 5, SF-21290 Rusko (FI). KARJALAINEN, Arja, Leena [FI/FI]; Tiilitie 15 C 24, SF-90650 Oulu (FI). ELORANTA, Maire, Marjatta [FI/FI]; Mäntyrinne 18, SF-90230 Oulu (FI). SALONEN, Jarmo, Sakari [FI/FI]; Tilhenkatu 21 L 241, SF-20600 Turku (FI). SIPILÄ, Hannu, Tapani [FI/FI]; Kerttulinkatu 14 B 38, SF-20500 Turku (FI). HAAPALINNA, Antti, Sakari [FI/FI]; Suurpäänkatu 35 A 14, SF-20610 Turku (FI).

(74) Agent: ORION CORPORATION; Orion-Farmos Pharmaceuticals, Patent Department, P.O. Box 65, SF-02101 Espoo (FI).

(81) Designated States: AT, AU, BG, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KR, LU, NL, NO, NZ, PL, PT, RO, RU, SE, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SUBSTITUTED IMIDAZOLE DERIVATIVES AND THEIR PREPARATION AND USE



(I)

(57) Abstract

This invention provides novel compounds of formula (I) wherein Y is $-CH_2-$ or -CO-; R_1 is F, Cl or OH; R_2 is H, F or Cl; and R_3 is H, CH_3 or CH_2CH_3, excluding 4-(5-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(4-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and their non-toxic acid addition salts and mixtures thereof. Processes for the preparation of these compounds are described, as are novel pharmaceutical compositions comprising at least one of the compounds or their salts. The compounds and their non-toxic salts exhibit valuable pharmacological activity and are highly selective and long acting antagonists at a_2-adrenoceptors. Their peroral bioavailability is good. The compounds are especially useful in the treatment of cognitive disorders.

FOR THE PURPOSES OF INFORMATION ONLY

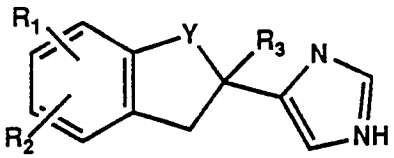
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SK	Slovak Republic
CI	Côte d'Ivoire	KZ	Kazakhstan	SN	Senegal
CM	Cameroon	LI	Liechtenstein	SU	Soviet Union
CS	Czechoslovakia	LK	Sri Lanka	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	UA	Ukraine
DK	Denmark	MG	Madagascar	US	United States of America
ES	Spain	ML	Mali	VN	Viet Nam
FI	Finland	MN	Mongolia		

SUBSTITUTED IMIDAZOLE DERIVATIVES AND THEIR PREPARATION AND USE

The present invention relates to novel 4(5)-substituted imidazole derivatives and their non-toxic salts, to their preparation, to pharmaceutical compositions containing them, and to their use.

The imidazole derivatives of this invention have the general formula:



(I)

wherein
Y is $-CH_2-$ or -CO-
R_1 is F, Cl or OH; R_2 is H, F or Cl; and R_3 is H, CH_3 or CH_2CH_3 and pharmaceutically acceptable thereof, excluding 4-(5-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(4-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole.

The most preferable compounds according to the present invention are those wherein R_1 is F, R_2 is hydrogen or F, especially hydrogen. Also preferable are compounds, wherein R_3 is hydrogen or CH_2CH_3 and Y is $-CH_2-$. As specific examples of such preferred compounds are mentioned 4-(2-ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole. These compounds are also valuable intermediates for the preparation of disubstituted indan-imidazole derivatives according to the invention.

The compounds of this invention are highly selective and long-acting antagonists of α_2-adrenoceptors and they have good peroral bioavailability. The compounds are especially valuable in the treatment of cognitive disorders.

Valuable α_2-adrenoceptor antagonists have been disclosed earlier e.g. in the European patent publications No. 183492, 247764 and 372954. PCT patent application No. 91/18886 discloses the use of some inden-imidazole derivatives, especially atipamezole, in the treatment of age-related memory impairment and other cognitive disorders. The compounds disclosed in these earlier patent applications, though some of them are very potent and selective α_2-adrenoceptor antagonists, have usually a very short duration of action. This causes no problems when the compounds are used during clinical procedures. However,

compounds with longer duration of action and good peroral bioavailability are necessary to obtain sufficient patient compliance. There are also indan-imidazole derivatives which have reported to have long duration of action e.g. those disclosed in EP 372954. However, such compounds are not so potent α_2-adrenoceptor antagonists as the compounds of the present invention.

α-Adrenoceptors can be divided on a pharmacological basis into two subclasses, viz α_1-and α_2-adrenoceptors (see e.g. Starke & Docherty, J. Cardiovasc. Pharmacol., I, Suppl. 1, 514-523, 1981). It is well established that while α_1-adrenoceptors are located postsynaptically, α_2-adrenoceptors are situated both at presynaptic nerve terminals and postsynaptically e.g. in vascular smooth muscle, platelets, pancreatic ß-cells, fat cells and central nervous system.

The presynaptic α_2-receptors modulate the release of noradrenaline by means of a negative feedback mechanism. Thus, if presynaptic α_2-adrenoceptors are stimulated (under physiological conditions by noradrenaline) noradrenaline release is inhibited. Blockade of these receptors by an α_2-antagonist, on the contrary, increases the release of noradrenaline. α_2-Adrenoceptor antagonism at presynaptic α_2-receptors can thus be expected to be of use in disease states which are believed to be connected with deficiency of noradrenaline available in the postsynaptic adrenoceptors. These diseases include e.g. endogeneous depresssion, age dependent memory impairment and other cognitive disorders, particularly Alzheimer's disease.

The best known pharmacodynamic effect mediated by postsynaptic α_2-adrenoceptors is the contraction of vascular smooth muscle. Blockade of peripheral postsynaptic α_2-adrenoceptors in blood vessels can thus be expected to dilate the vessel and lead to decrease in the blood pressure. α_2-Blockers may thus be valuable as antihypertensive agents.

Glucose and lipid metabolism are also regulated by an inhibitory mechanism involving α_2-adrenoceptors. An α_2-antagonist may thus be of use in diabetes and obesity.

The following compounds of the invention were tested.

Table 1.

No. Name

1. 4-(2-Ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

2. 4-(5-Fluoro-2,3-dihydro-2-methyl-1H-inden-2-yl)-1H-imidazole

3. 4-(2-Ethyl-5,6-difluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

4. 2-Ethyl-6-fluoro-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one

5. 6-Chloro-2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one

6. 4-(4-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

7. 4-(5-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

8. 2-Ethyl-2-(1H-imidazol-4-yl)-5-indanol

The pharmacological activity of the compounds of the present invention was determined as follows:

1. α_2-Antagonism in vitro

α_2-Antagonism was determined by means of isolated, electrically stimulated mouse vas deferens preparation (Marshall et al., Br.J. Pharmac. 62, 147, 151, 1978). In this model, α_2-agonist (detomidine) blocks electrically stimulated muscular contractions and the effect of the α_2-antagonist is seen by administering it prior to the agonist and by determining its pA_2 value. The known α_2-antagonist atipamezole was used as a reference substance.

To obtain information also on the selectivity of the antagonist between α_1- and α_2-receptors, its ability to inhibit or stimulate α_1-receptors was determined by means of isolated epididymal portion of rat vas deferens. The reference substances were now phenylephrine, a known α_1-agonist, and prazosin, a known α_1-antagonist. To determine α_1-antagonism, muscular contraction was induced by phenylephrine and the pA_2 value of the studied compound was determined as above. α_1-Agonist effect is presented as the pD_2 value (negative logarithm of the molar concentration of the compound producing 50 percent of maximal contraction). Examples of the results are given in Table 2.

Table 2.

Compound	α_2-Antagonism (pA2 vs detomidine)	α_1-Antagonism (pA2 vs phenyl-ephrine)	α_1-Agonism (pD2)
	mouse vas deferens	rat was deferens	rat was deferens
1.	8.2	no effect	no effect
2.	7.3	not measured	not measured
3.	7.2	not measured	not measured
4.	5.9	no effect	no effect
5.	6.6	not measured	not measured
6.	8.1	-	6.5, full agonist
7.	8.0	-	5.5, partial agonist
8.	7.2	not measured	not measured
atipamezole	8.1	5.0	no effect

2. α_2-Adrenoceptor antagonism in vivo

It is known that in the rat α_2-agonists induce dilatation of the pupil (mydriasis) which effect is transmitted via postsynaptic α_2-receptors in the central nervous system. In anaesthetized rat, a standard dose of an α_2-agonist, detomidine, was administered intravenously. Thereafter increasing doses of the studied antagonists were injected intravenously and the reversal of detomidine-induced mydriasis was followed. The ED_{50} value of the antagonist, i.e. the dose producing a 50 per cent reversal, was determined. Examples of the results of this test are presented in Table 3.

The duration of the α_2-blocking action of the compounds was determined as follows: the antagonists were administered orally at equipotent doses to groups of 4 rats 1, 2, 4, 7 or 16 hours before

induction of anaesthesia and challenge with cumulative i.v. dosing of detomidine. By calculating the percentage antagonism of the mydriatic effect of 0,1 mg/kg detomidine for each pretreatment group, a time-effect relationship was established. This in turn permitted the measurement of the time taken for the antagonist effect to fall by half. Results are shown in table 3.

The relative bioavailability of the antagonists when administered orally was evaluated by comparing the potency of their α_2-blocking effect after peroral and parenteral administration. The antagonists were administered at equipotent doses (0.3 to 3 mg/kg) to groups of rats 1 hour before induction of anaesthesia and challenge with detomidine as described above in relation to the measurement of duration of action. The results are shown in Table 3.

Table 3

Compound	α_2-Antagonism ED_{50} µg/kg iv)	$t_{1/2}$ of α_2-antagonism	Peroral bioavailability
1.	15	3	81
4.	300	6	89
7.	10	7	80
Atipamezole	10	2	56

3. Effects on memory

The effects of atipamezole, MPV-1743 A III (compound 7) and MPV-1730 B III (compound 4) on learning and memory in linear arm maze task in rats were studied. The linear arm maze is a modified version of radial arm maze, which is a generally used memory test in rats. Atipamezole hydrochloride (0.3 mg/kg s.c.), MPV-1730 B III hydrochloride (3 mg/kg p.o.) and MPV-1743 A III hydrochloride (0.3 mg/kg s.c.) were dissolved in distilled water. Water was also used as control. All injections were made in a volume 1 ml/kg.

Apparatus: The maze was a wooden platform in a shape of two crosses one after another. The stem (starting arm) was 90 cm long and 12 cm wide. The five other arms (goal arms) were 50 cm long and 12 cm wide. Four goal arms were situated perpendicularly to the stem and to the fifth arm which located opposite to the stem. On either side of the stem and the arms were edges, 2.0 cm high. At the end of each goal arm

a hole 1 cm deep and 3 cm in diameter, served as a food cup. The starting platform (20 x 20 cm) was separated from the stem by a quillotine door. The door was 12 cm high and 7 cm wide. The door frame was 20 cm high and 20 cm wide. The maze was elevated 31 cm above the floor, in a low-lighted test room which contained other objects as well as the test apparatus. The holes at the end of the goal arms were baited with three pellets of prize food (45 mg pellets Bio Serve Inc.).

Procedures: Two days prior to training, animals were placed on a food deprivation scedule that reduces their body weights to 90% of initial weights. During these days the rats were habituated to handling (three times/day), test room and prize food. On the second day they were also habituated to the unbaited maze: three to five animals from the same cage at the same time for ten minutes. On the third day the goal arms were baited, and the teaching trial, one rat at a time, was carried out. The rat received drug or distilled water and 60 minutes later it was placed in the starting platform. After ten seconds the door was opened and the rat was allowed to explore the maze until all the baits were found. The time to find all the baits and reentries made into already visited arms was recorded. This time every rat was allowed to stay in the maze at least for five minutes. On the next day the proper memory and learning testing began and continued for four days (testing days 1 to 4). Rats were given eight trials, two per day. Inter trial interval was 50 minutes. Drugs or distilled water were administered 30 minutes before the first trial of the day. Otherwise testing trials were identical to the teaching trial. All the observations were done blind so that test solutions were in coded flasks.

Statistical analysis: The results were expressed as mean time/trial/day (seconds) and mean errors/trial/day. The analysis of variance for the repeated measurements (ANOVA) was used to compare the drugs' and the testing days' effects on learning and memory.

Results: The effects of atipamezole, MPV-1743 A III (= compound no. 7) and MPV-1730 B III (= compound no. 4) on learning and memory are presented in Figure 1, Figure 2 and Figure 3 respectively. All tested drugs decreased number of errors i.e. reentrients into arms already visited during the same trial. This indicates an effect on working memory. All the drugs also decreased the time to solve the task. It is considered as an effect on learning and on speed to make correct choices. The number of errors and time decreased day to day also in the control group which indicates learning during testing. There were no any group x day- interaction, which means that the effect of the drugs did not depend on the testing day. These results suggest that atipamezole, MPV-1743 A III and MPV-1730 B III have learning and memory enhancing effects on adult rats.

The compounds of this invention react with organic and inorganic acids to form many pharmaceutically usable acid addition salts, as, for instance, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like. The salts have the same therapeutic activity as the base.

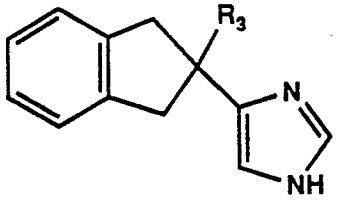
The compounds and their non-toxic, pharmaceutically acceptable acid addition salts may be administered orally, parenterally or intravenously. In the treatment of cognitive disorders the compounds are preferably administered orally at a daily dose of 0,1 to 10 mg/kg, preferably 0.2 to 1 mg/kg.

The pharmaceutical carriers which are typically employed with the compound of the invention may be solid or liquid and are generally selected with the planned manner of administration in mind. Choosing the auxiliary ingredients for the formulation is routine for those of ordinary skill in the art. It is evident that suitable solvents, gel forming ingredients, dispersion forming ingredients, colors etc are used in a normal way.

The acute toxicity (LD_{50}) using mice for the compounds of the invention is below 50 mg/kg (p.o.). For example, the LD_{50} for 7-(4-(5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole) is 100 mg/kg (p.o.).

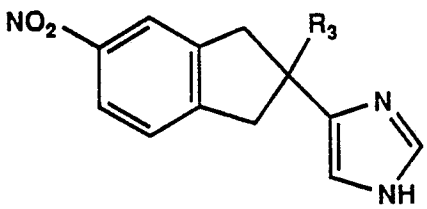
The compounds of formula (I) can be prepared according to the following methods:

A compound of formula (II)



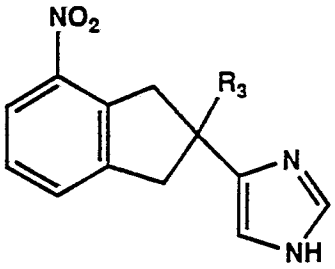
(II)

where R_3 is as defined above is nitrated with strong nitrating agent able to form the nitronium ion $^{+}NO_2$, preferably with ureanitrate ($H_2NCONH_2 \times HNO_3$) in the presence of sulfuric acid, to give mainly the compound of formula (III)



(III)

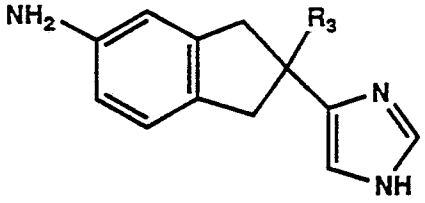
but also a small amount of the compound of formula (IV), which compounds may be optionally separated



(IV)

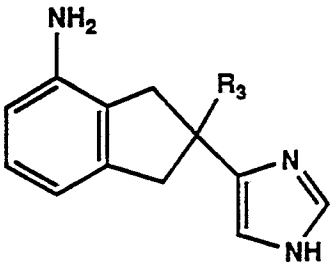
The nitro group of compounds (III) or (IV) is further reduced to the corresponding NH_2 group e.g. by catalytic hydrogenation using molecular hydrogen. Preferable catalysts are e.g. PtO_2 or Pd/C. The amino-substituted compounds so obtained can be separated from each other.

The amino substituted compounds



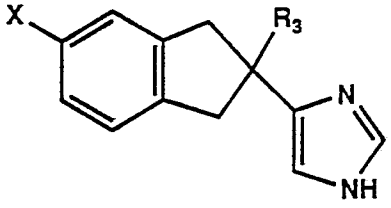
(V)

and

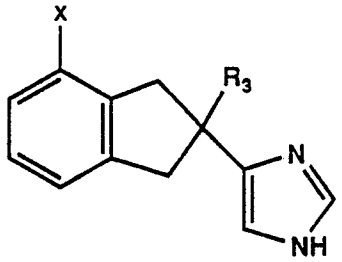


(VI)

are converted to their corresponding diazonium salts with nitrous acid which reagent is generated in the presence of the amine (V or VI) by the action of mineralic acid, preferably fluoroboric acid (HBF_4) on sodium nitrite at lowered temperature, preferably at about 0°C. The diazonium fluoroborate so formed can be termally decomposed to yield the fluoride (VII) or (VIII), boron trifluoride and nitrogen.



(VII)

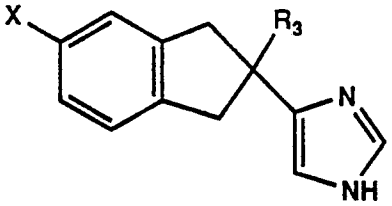


(VIII)

wherein X is F.

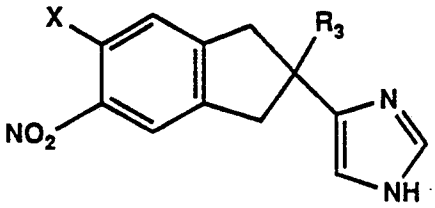
The corresponding chlorosubstituted compounds can be formed by reacting the amine (V or VI) with hydrochloric acid and sodium nitrite at lowered temperature and then by reacting the diazonium group with a metal chloride, preferably copper(I) chloride, in concentrated hydrochloric acid at elevated temperature.

The monohalogenated compound of formula (VII)



(VII)

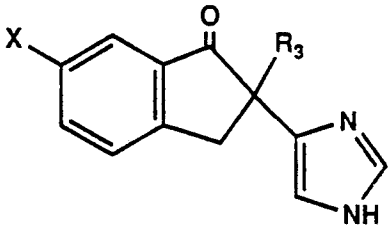
where X is F or Cl can further be nitrated by reaction with e.g. ureanitrate in sulfuric acid to give compound (IX)



(IX)

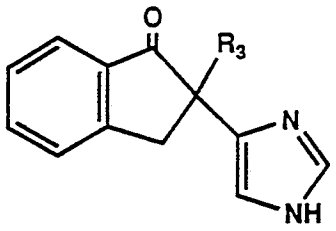
where the nitro group further can be replaced by a halogen via an amino group as described above to give a compound of formula (I) where R_1 and R_2 both are halogen.

Compounds of formula (I) where Y is CO, R_1 is F or Cl in the 6-position (X)



(X)

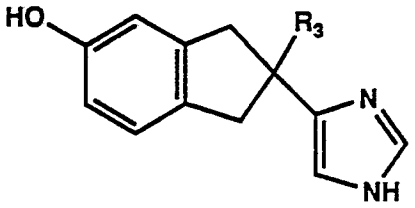
(X = F or Cl) can be achieved by nitrating a starting material of the formula XI



(XI)

with e.g. ureanitrate in sulfuric acid and replacing the nitro group by an amino group which further is replaced by halogen according to the methods described above. Another halogen atom can further be introduced into the 4-position of the aromatic ring of compound (X) by nitration of the compound with e.g. ureanitrate in sulfuric acid, hydrogenation of the nitro group to an amino group, and finally replacing the amino group by a halogen according to the methods described above.

A compound of the formula XII



(XII)

can be prepared by reacting the compound of formula (V) e.g. with sodium nitrite in the presence of concentrated sulfuric acid at low temperature. The diazonium salt is then termally decomposed to yield the compound of formula (XII).

Further compounds of the invention may be prepared by analogy with the processes desribed in EP-A-183492.

In the examples below, where ^{1}H and ^{13}C NMR spectrum shifts are presented, the NMR spectra were obtained on a Bruker AC 300 P spectrometer using tetramethylsilane as the internal reference, from which the presented chemical shifts (δ, ppm) were measured downfield. The letters s, d, t, q and m are used to indicate a singlet, doublet, triplet, quartet or multiplet, respectively. In the same connection, the number of hydrogen atoms is also stated. The spectra of the compounds as bases were recorded in deuterium methanol or

deuterium chloroform, while the values for compounds as hydrochlorides were determined in deuterium methanol. The mass spectra were recorded on a Kratos MS 80 RF Autoconsole mass spectrometer.

Example 1

4-(2-ETHYL-5-FLUORO-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

4-(2-Ethyl-2,3-dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole

4-(2-Ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole (Karjalainen, A. J. et.al. U.S. 4,689,339; 3.00 g, 0.0141 mol) was added to 15 ml of concentrated sulphuric acid at 0°C. Ureanitrate (1.74 g, 0.0141 mol) was added in small portions at 0°C. After the reaction the solution was poured into ice water. The solution was made alkaline with sodium hydroxide and was extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and evaporated. The yield of 4-(2-ethyl-2,3-dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole was 3.59 g (99 %). The hydrochloride salt of the product was prepared in dry hydrogen chloride - ethyl acetate.

MS: 257 (22, $M^{+\cdot}$), 228 (100, M-CH_2CH_3), 182 (27, 228-NO_2)

The hydrochloride salt, ^1H NMR (300 MHz, CD_3OD): δ 0.82 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.97 (2H, q, J 7 Hz, $C\underline{H}_2CH_3$), 3.31 and 3.41 (4H, AB q, J_{AB} 17 Hz, the indan ring H_2-1 and H_2-3), 7.44 (1H, s, im-5), 7.46 (1H, d, H-7), 8.05 (1H, d, J 8 Hz, H-6), 8.10 (1H, s, H-4), 8.92 (1H, s, im-2)

4-(5-Amino-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

A solution of 4-(2-ethyl-2,3-dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole (10.25 g, 0.03988 mol) in ethanol (150 ml) was hydrogenated over PtO_2 (1 g) at 3 atm pressure. When the uptake of hydrogen ceased the reaction mixture was filtered and evaporated to dryness to give 4-(5-amino-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole (8.2 g, 91 %).

The product was purified by flash chromatography eluting with methylene chloride - methanol mixture (9.5:0.5). The hydrochloride salt of the product was made with dry hydrogen chloride in dry ethyl acetate - ether; mp. 145-152°C.

MS: 227 (50, $M^{+\cdot}$), 212 (15, M-CH_3), 198 (100, M-CH_2CH_3)

Base, ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.87 (2H, q, J 7 Hz, $C\underline{H}_2CH_3$), 2.96 and 3.11 (2H, AB q, J_{AB} 15 Hz, the indan ring H_2-1 or H_2-3), 2.98 and 3.13 (2H, AB q, J_{AB} 16 Hz, the indan ring H_2-1 or H_2-3), 6.48 (1H, dd, ^{3}J 8 Hz, ^{4}J 2 Hz, H-6), 6.54 (1H, broad s, H-4), 6.73 (1H, s, im-5), 6.95 (1H, d, ^{3}J 8 Hz, H-7), 7.48 (1H, s, im-2)

The hydrochloride salt, ^{13}C NMR (CD_3OD): δ 9.82 (q), 33.35 (t), 44.15 (t), 44.53 (t), 48.92 (s), 117.34 (d), 120.47 (d), 122.64 (d), 127.12 (d), 130.63 (s), 135.67 (d), 140.69 (s), 143.71 (s), 144.97 (s)

4-(2-Ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

The flask containing fluoboric acid (48 wt.% solution in water, 25 ml) and 5.63 g (0.0248 mol) of 4-(5-amino-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was placed in an ice-salt bath and cooled to 0°C. A solution of 2.6 g (0.0377 mol) of sodium nitrite in 5 ml of water was run in slowly while the temperature was kept at 0°C. After the addition the mixture was stirred for an hour at 0°C and then for an hour at the room temperature. The reaction mixture was evaporated twice to dryness with toluene.

The thermal decomposition was carried out in the flask which was heated with an electric heating mantle. When the generation of white fumes of boron trifluoride ceased the heating was stopped.

The crude product was dissolved in methanol, the solution was filtered and evaporated to dryness.

The product was purified by flash chromatography (the eluent methylene chloride - methanol 9.5:0.5). The hydrochloride salt of the product was prepared in ethyl acetate; mp. 152-154°C.

MS: 230 (27, $M^{+\cdot}$), 201 (100, M-CH_2CH_3), 133 (14), 100 (15)

The hydrochloride salt, ^{1}H NMR (300 MHz, CD_3OD): δ 0.80 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.93 (2H, q, J 7 Hz, $C\underline{H}_2CH_3$), about 3.11-3.30 (4H, m, the indan ring H_2-1 and H_2-3), 6.87 (1H, m, H-6), 6.96 (1H, dd, $^3J_{HF}$ 9 Hz, $^4J_{HH}$ 2 Hz, H-4), 7.18 (1H, dd, $^3J_{HH}$ 8 Hz, $^4J_{HF}$ 5 Hz, H-7), 7.37 (1H, d, J 1 Hz, im-5), 8.87 (1H, d, J 1 Hz, im-2)

The hydrochloric salt, ^{13}C NMR (CD_3OD): δ 9.87 (CH_3), 33.45 ($\underline{C}H_2CH_3$), 43.99 (C-1), 44.74 ($^4J_{CCCCF}$ 2 Hz, C-3), 49.14 (C-2), 112.14 ($^2J_{CCF}$ 23 Hz, C-4), 114.55 ($^2J_{CCF}$ 23 Hz, C-6), 117.28 (im-5), 126.78 ($^3J_{CCCF}$ 9

Hz, C-7), 135.60 (im-2), 137.93 ($^4J_{CCCCF}$ 3 Hz, C-7a), 141.15 (im-4), 144.72 ($^3J_{CCCF}$ 8 Hz, C-3a), 163.75 (J_{CF} 242 Hz, C-5)

Example 2

4-(5-FLUORO-2,3-DIHYDRO-2-METHYL-1H-INDEN-2-YL)-1H-IMIDAZOLE

The procedure of Example 1 was also used to synthesize 4-(5-fluoro-2,3-dihydro-2-methyl-1H-inden-2-yl)-1H-imidazole and its intermediates from 4-(2,3-dihydro-2-methyl-1H-inden-2-yl)-1H-imidazole (Karjalainen, A. J. et.al. U.S. 4,689,339).

4-(2,3-Dihydro-2-methyl-5-nitro-1H-inden-2-yl)-1H-imidazole

MS: 243 (50, $M^{+\cdot}$), 228 (100, M-CH_3), 182 (30)

Base, ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ 1.49 (3H, s, CH_3), 3.05 and 3.44 (4H, AB q, J_{AB} 16 Hz, H_2-1 and H_2-3), 6.79 (1H, d, J 1 Hz, im-5), 7.36 (1H, d, J 9 Hz, H-7), 7.56 (1H, d, J 1 Hz, im-2), 8.04 (1H, d, J 9 Hz, H-6), 8.06 (1H, s, H-4)

4-(5-Amino-2,3-dihydro-2-methyl-1H-inden-2-yl)-1H-imidazole

MS: 213 (90, $M^{+\cdot}$), 198 (100, M-CH_3)

Base, ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ 1.42 (3H, s, CH_3), 2.87 and 3.21 (2H, AB q, J_{AB} 16 Hz, the indan ring H_2-1 or H_2-3), 2.86 and 3.18 (2H, AB q, J_{AB} 15 Hz, the indan ring H_2-1 or H_2-3), 6.51 (1H, dd, ^{3}J 8 Hz, ^{4}J 2 Hz, H-6), 6.55 (1H, d, J 2 Hz, H-4), 6.74 (1H, d, J 1 Hz, im-5), 6.98 (1H, d, ^{3}J 8 Hz, H-7), 7.52 (1H, J 1 Hz, im-2)

4-(5-Fluoro-2,3-dihydro-2-methyl-1H-inden-2-yl)-1H-imidazole

The hydrochloride salt: Mp. 188-190°C

MS: 216 (50, $M^{+\cdot}$), 201 (100, M-CH_3), 133 (18)

The hydrochloride salt, ^{1}H NMR (300 MHz, CD_3OD): δ 1.51 (3H, s, CH_3), 3.03-3.12 and 3.26-3.36 (4H, H_2-1 and H_2-3), 6.87-6.99 (2H, m, H-4 and H-6), 7.20 (1H, m, H-7), 7.38 (1H, s, im-5), 8.85 (1H, J 1 Hz, im-2)

Example 3

2-ETHYL-2-(1H-IMIDAZOL-4-YL)-5-INDANOL

In a flask were placed 0.76 g (0.00334 mol) of 4-(5-amino-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole, 2.7 ml of water and 0.76 ml of concentrated sulfuric acid. A solution was cooled to 0°C and a solution of 0.47 g (0.00681 mol) of sodium nitrite in 1.52 ml of water was added so that the temperature during the diazotization was maintained at 0-5°C. Stirring was continued for one hour at 0-5°C.

While the diazotization was in progress, 2.28 ml of concentrated sulfuric acid was added to 1.9 ml of water in a flask and the solution was heated to boiling (160°C). The solution from the diazotization was then added at such a rate that the acid mixture boiled. Boiling was continued for one hour. Water was poured into the cooled mixture. The pH value of the solution was adjusted to 7-8 and the precipitated impurities were filtered off. The water solution was extracted with several portions of ethyl acetate and the combined organic extractions were washed with water, dried with Na_2SO_4 and evaporated to dryness. The crude yield of the product was 0.6 g (79%). Purification was performed by flash chromatography (the eluent methylene chloride -methanol 9.5:0.5). The hydrochloride salt of the product was prepared in ethyl acetate; mp. 193-196°C.

MS: 228 (38, $M^{+\cdot}$), 213 (12, M-CH_3), 199 (100, M-CH_2CH_3)

The hydrochloride salt, 1H NMR (300 MHz, CD3OD): δ 0.79 (3H, t, J 7 Hz, CH2CH3), 1.91 (2H, q, J 7 Hz, CH2CH3), 3.06 and 3.15 (2H, AB q, JAB 15 Hz, the indan ring H2-1 or H2-3), 3.09 and 3.18 (2H, AB q, JAB 16 Hz, the indan ring H2-1 or H2-3), 6.57 (1H, dd, 3J 8 Hz, 4J 2 Hz, H-6), 6.65 (1H, d, 4J 2 Hz, H-4), 7.00 (1H, d, 3J 8 Hz, H-7), 7.31 (1H, d, J 1 Hz, im-5), 8.80 (1H, s, im-2)

Example 4

2-ETHYL-6-FLUORO-2,3-DIHYDRO-2-(1H-IMIDAZOL-4-YL)-1H-INDEN-1-ONE

2-Ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-6-nitro-1H-inden-1-one

The nitro derivative of 2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one (Karjalainen, A. J. et.al. U.S. 4,689,339) was prepared in the way described in Example 1. The yield was 100 %. Mp. of the hydrochloride salt of the product was 226-228°C.

MS: 271 (33, $M^{+\cdot}$), 256 (12, M-CH_3), 242 (100, M-CH_2CH_3), 196 (32, 242-NO_2)

The hydrochloride salt, ^{1}H NMR (300 MHz, CD_3OD): δ 0.87 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.96-2.20 (2H, m, $C\underline{H_2}CH_3$), 3.66 and 3.78 (2H, AB q, J_{AB} 19 Hz, the indan ring H_2-3), 7.65 (1H, d, J 1 Hz, im-5), 7.91 (1H, d, ^{3}J 9 Hz, H-4), 8.50 (1H, d, ^{4}J 2 Hz, H-7), 8.58 (1H, dd, ^{3}J 9 Hz, ^{4}J 2 Hz, H-5), 8.98 (1H, d, J 1 Hz, im-2)

6-Amino-2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one

To 7.20 g (0.0265 mol) of 2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-6-nitro-1H-inden-1-one dissolved in 70 ml of ethanol was added 0.7 g of 10 % palladium on carbon and the mixture was shaken in an atmosphere of hydrogen at the room temperature. When the reduction came to a standstill the catalyst was removed. The filtrate was concentrated to give 6-amino-2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one (5.96 g, 93 %). The product was purified by flash chromatography eluting with methylene chloride - methanol mixture (9.5:0.5).

MS: 241 (36 %, $M^{+\cdot}$), 212 (100 %, M-CH_2CH_3)

Base, ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.84-2.04 (2H, m, $C\underline{H_2}CH_3$), 3.20 and 3.55 (2H, AB q, J_{AB} 17 Hz, the indan ring H_2-3), 6.92 (1H, s, im-5), about 6.9 (1H, m, H-5), 6.97 (1H, s, H-7), 7.25 (1H, d, ^{3}J 10 Hz, H-4), 7.51 (1H, s, im-2)

Base, ^{13}C NMR (CD_3OD): δ 9.42 (q), 31.85 (t), 38.88 (t), 55.15 (s), 108.77 (d), 117.39 (d), 125.28 (d), 127.90 (d), 136.48 (d), 137.67 (s), 140.37 (s), 144.48 (s), 149.07 (s), 188.78 (s)

2-Ethyl-6-fluoro-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one

2-Ethyl-6-fluoro-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one was prepared in the way described in Example 1. The product was purified by flash chromatography (the eluent methylene chloride methanol 9.5:0.5). Yield after purification was 75 %. The hydrochloride salt of the product was prepared in ethyl acetate; mp. 167-168°C.

MS: 244 (27, $M^{+\cdot}$), 215 (100, M-CH_2CH_3), 187 (10), 149 (14), 133 (18), 107 (12), 85 (14), 71 (12), 69 (10), 57 (24)

The hydrochloride salt, ^{1}H NMR (300 MHz, CD_3OD): δ 0.85 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.93-2.20 (2H, m, $\underline{CH_2}CH_3$), 3.48 and 3.60 (2H, AB q, J_{AB} 17 Hz, the indan ring H_2-3), 7.43 (1H, dd, $^3J_{HF}$ 8 Hz, $^4J_{HH}$ 3 Hz, H-7), 7.53 (1H, m, $^4J_{HH}$ 3 Hz, H-5), 7.59 (1H, d, J 1 Hz, im-5), 7.68 (1H, dd, $^3J_{HH}$ 8 Hz, $^4J_{HF}$ 5 Hz, H-4), 8.93 (1H, d, J 1 Hz, im-2)

The hydrochloride salt, ^{13}C NMR (CD_3OD): δ 9.32 ($CH_2\underline{C}H_3$), 32.35 ($\underline{C}H_2CH_3$), 37.91 (C-3), 54.18 (C-2), 110.89 ($^2J_{CCF}$ 22 Hz, C-7), 117.83 (im-5), 124.83 ($^2J_{CCF}$ 24 Hz, C-5), 129.97 ($^3J_{CCCF}$ 8 Hz, C-4), 135.38 (im-4), 136.24 (im-2), 137.30 ($^3J_{CCCF}$ 7 Hz, C-7a), 149.57 ($^4J_{CCCCF}$ 2 Hz, C-3a), 164.12 (J_{CF} 248 Hz, C-6), 193.93 (C=O)

Example 5

6-FLUORO-2,3-DIHYDRO-2-(1H-IMIDAZOL-4-YL)-2-METHYL-1H-INDEN-1-ONE

6-Fluoro-2,3-dihydro-2-(1H-imidazol-4-yl)-2-methyl-1H-inden-1-one and its intermediates were synthesized from 2,3-dihydro-2-(1H-imidazol-4-yl)-2-methyl-1H-inden-1-one (Karjalainen, A. J. et.al. U.S. 4,689,339) according to the procedure used in Example 4.

2,3-Dihydro-2-(1H-imidazol-4-yl)-2-methyl-6-nitro-1H-inden-1-one

MS: 257 (100, $M^{+\cdot}$), 242 (98, M-CH_3), 228 (65)

Base, ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ 1.62 (3H, s, CH_3), 3.32 and 3.94 (2H, AB q, J_{AB} 18 Hz, H_2-3), 6.96 (1H, s, im-5), 7.52 (1H, s, im-2), 7.70 (1H, d, J 9 Hz, H-5), 8.51 (1H, dd, ^{3}J 9 Hz, ^{4}J 2 Hz, H-5), 8.60 (1H, d, J 2 Hz, H-7)

6-Amino-2,3-dihydro-2-(1H-imidazol-4-yl)-2-methyl-1H-inden-1-one

MS: 227 (100, $M^{+\cdot}$), 212 (85, M-CH_3), 198 (50)

Base, ^{1}H NMR (300 MHz, CD_3OD): δ 1.52 (3H, s), 3.07 and 3.52 (2H, AB q, J_{AB} 17 Hz, H_2-3), 6.93 (1H, s, im-5), 6.98 (1H, d, J 2 Hz, H-7), 7.03 (1H, dd, ^{3}J 8 Hz, ^{4}J 2 Hz, H-5), 7.27 (1H, d, J 8 Hz, H-4), 7.55 (1H, s, im-2)

6-Fluoro-2,3-dihydro-2-(1H-imidazol-4-yl)-2-methyl-1H-inden-1-one

The hydrochloride salt: Mp. 164-167°C

MS: 230 (100, $M^{+\cdot}$), 215 (95, M-CH_3), 201 (80), 187 (25), 174 (25), 133 (25)

The hydrochloride salt, ^1H NMR (300 MHz, CD_3OD): δ 1.65 (3H, s, CH_3), 3.38 and 3.65 (2H, AB q, J_{AB} 17 Hz, H_2-3), 7.45-7.66 (3H, m, H-4, H-5, H-7), 7.54 (1H, s, im-5), 8.85 (1H, s, im-2)

Example 6

6-CHLORO-2-ETHYL-2,3-DIHYDRO-2-(1H-IMIDAZOL-4-YL)-1H-INDEN-1-ONE

In the flask were placed 2.95 g (0.0122 mol) of 6-amino-2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one, 4.5 ml of water and 4.5 ml of concentrated hydrochloric acid. This solution was cooled to 0°C and a solution of 0.84 g (0.0122 mol) of sodium nitrite in 3 ml of water was run in slowly while the temperature was kept below 5°C. After the addition the mixture was stirred for one hour at 0°C.

In another flask 1.46 g (0.0147 mol) of copper(I) chloride was dissolved in the mixture of water (6 ml) and concentrated hydrochloric acid (4.5 ml) and the solution was chilled in an ice-water bath.

The ice-cold diazonium solution was added, with stirring, to the copper(I) chloride solution while the temperature was kept at 0°C. After the addition the stirring was continued for thirty minutes at 0°C. The temperature was then let to increase slowly to the room temperature. After this the mixture was heated for 1.5 hours at 70°C.

After the mixture was cooled, water was added and the solution was made alkaline. The product was extracted into ethyl acetate, washed with water and evaporated. The crude product was purified by flash chromatography (the eluent methylene chloride - methanol 9.5:0.5). The hydrochloride salt of 6-chloro-2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one was prepared in ethyl acetate; mp. 198-201°C.

MS: 260 and 262 (22 and 8, $M^{+\cdot}$), 231 and 233 (100 and 34, M-CH_2CH_3)

The hydrochloride salt, ^1H NMR (300 MHz, CD_3OD): δ 0.84 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.93-2.19 (2H, m, $C\underline{H}_2CH_3$), 3.48 and 3.60 (2H, AB q, J_{AB} 18 Hz, the indan ring H_2-3), 7.57 (1H, d, J 1 Hz, im-5), 7.64 (1H, distorted

d, J 8 Hz, H-4), 7.73 (1H, s, H-7), 7.74 (1H, distorted d, H-5), 8.90 (1H, s, im-2)

Example 7

4-(5-FLUORO-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

4-(2,3-Dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole

Concentrated sulphuric acid (11 ml) was cooled to -10°C and the mixture of 4-(2,3-dihydro-1H-inden-2-yl)-1H-imidazole hydrochloride (Karjalainen, A. J. et.al. U.S. 4,689,339; 2.70 g, 0.0122 mol) and ureanitrate (1.50 g, 0.0122 mol) was added in small portions to the acid solution at -10°C. After the reaction the solution was poured onto ice. The solution was made alkaline and extracted three times with ethyl acetate. The organic extracts were combined, dried and evaporated to dryness. The yield 1.28 g, 91 %.

MS: 229 (100, $M^{+\cdot}$), 228 (55, M-H), 214 (19), 212 (26), 201 (12), 183 (16, M-NO_2), 182 (61, 228-NO_2), 168 (14), 153 (13), 154 (16), 129 (10), 128 (18), 127 (16), 115 (16), 91 (12 %), 77 (12), 68 (19)

Base, ^{1}H NMR (300 MHz, $CDCl_3$ + one drop of CD_3OD): δ 3.18 (2H, dd, J_{gem} 16 Hz, J_{vis} 8 Hz, the indan ring one H-1 and one H-3), 3.39 (2H, dd, J_{gem} 16 Hz, J_{vis} 8 Hz, the indan ring another H-1 and another H-3), 3.80 (1H, quintet, J_{vis} 8 Hz, the indan ring H-2), 6.80 (1H, s, im-5), 7.34 (1H, d, J 8 Hz, H-7), 7.57 (1H, s, im-2), 8.05 (1H, d, J 8 Hz, H-6), 8.06 (1H, s, H-4)

4-(5-Amino-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

Reduction of 4-(2,3-dihydro-5-nitro-1H-inden-2-yl)-1H-imidazole to 4-(5-amino-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was carried out in the way described in Example 4. Yield was 94 %. Purification of the product was performed by flash chromatography (the eluent methylene chloride - methanol 9.5:0.5).

MS: 199 (100, $M^{+\cdot}$), 198 (34, M-H), 184 (32), 171 (12), 157 (12), 149 (21), 131 (21), 130 (25), 99 (14), 98 (14), 77 (10), 69 (18)

Base, ^{1}H NMR (300 MHz, CD_3OD): δ 2.85-2.96 (2H, m, one H-1 and one H-3), 3.09-3.18 (2H, m, another H-1 and another H-3), 3.57 (1H, quintet, J 8 Hz, H-2), 6.54 (1H, dd, ^{3}J 8 Hz, ^{4}J 2 Hz, H-6), 6.63 (1H, s, H-4), 6.78 (1H, s, im-5), 6.93 (1H, d, J 8 Hz, H-7), 7.57 (1H, s, im-2)

4-(5-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

4-(5-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was prepared from 4-(5-amino-2,3-dihydro-1H-inden-2-yl)-1H-imidazole in the way described in Example 1. The yield of the crude product was 99 %. The product was purified by flash chromatography (the eluent methylene chloride - methanol 9.5:0.5). The hydrochloride salt of the product was prepared in ethyl acetate; mp. 189-191°C.

MS: 202 (100, $M^{+\cdot}$), 201 (64, M-H), 187 (51), 174 (25), 160 (16), 147 (14), 146 (17), 133 (32), 132 (16), 100 (10)

The hydrochloride salt, ^1H NMR (300 MHz, CD_3OD): δ 3.01-3.14 (2H, m, one H-1 and one H-3), 3.34-3.45 (2H, m, another H-1 and another H-3), 3.84 (1H, quintet, J 8 Hz, H-2), 6.90 (1H, m, H-6), 6.99 (1H, d, $^3J_{HF}$ 9 Hz, H-4), 7.24 (1H, dd, $^3J_{HH}$ 8 Hz, $^4J_{HF}$ 5 Hz, H-7), 7.37 (1H, s, im-5), 8.83 (1H, s, im-2)

The hydrochloride salt, ^{13}C NMR (CD_3OD): δ 37.37 (C-2), 38.94 (C-1), 39.75 ($^4J_{CCCCF}$ 2 Hz, C-3), 112.42 ($^2J_{CCF}$ 23 Hz, C-4), 114.65 ($^2J_{CCF}$ 23 Hz, C-6), 116.18 (im-5), 126.63 ($^3J_{CCCF}$ 9 Hz, C-7), 135.15 (im-2), 138.27 ($^4J_{CCCCF}$ 2 Hz, C-7a), 138.47 (im-4), 145.05 ($^3J_{CCCF}$ 8 Hz, C-3a), 163.80 ($^2J_{CF}$ 242 Hz, C-5)

Example 8

4-(4-FLUORO-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

4-(4-Amino-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

In the nitration of 4-(2,3-dihydro-1H-inden-2-yl)-1H-imidazole (Example 7) also a small amount of 4-(2,3-dihydro-4-nitro-1H-inden-2-yl)-1H-imidazole was formed. After the catalytic hydrogenation the 4-amino isomer was isolated and purified by flash chromatography.

MS: 199 (100, $M^{+\cdot}$), 198 (40, M-H), 184 (29), 183 (13), 171 (10), 149 (10), 131 (20), 130 (28), 69 (20)

4-(4-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

4-(4-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was prepared according to the fluorination method of Example 1. The product was purified by flash chromatography (the eluent methylene chloride methanol 9.5:0.5). The hydrochloride salt of the product was prepared in ethyl acetate; mp. 180-183°C.

MS: 202 (100, $M^{+\cdot}$), 201 (72, M-H), 187 (38), 174 (24), 160 (12), 147 (12), 146 (16), 134 (15), 133 (27), 100 (11), 68 (12)

The hydrochloride salt, ^1H NMR (300 MHz, CD_3OD): δ 3.04-3.18 (2H, m, one H-1 and one H-3), 3.36-3.53 (2H, m, another H-1 and another H-3), 3.86 (1H, quintet, J 8 Hz, H-2), 6.91 (1H, t, $^3J_{HH}$ 9 Hz, H-6), 7.09 (1H, d, $^3J_{HH}$ 9 Hz, H-7), 7.18-7.25 (1H, m, H-5), 7.39 (1H, s, im-5), 8.83 (1H, s, im-2)

Example 9

4-(2-ETHYL-5,6-DIFLUORO-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

4-(2-Ethyl-5-fluoro-2,3-dihydro-6-nitro-1H-inden-2-yl)-1H-imidazole

4-(2-Ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole (4.56 g, 0.0198 mol) was added to 24 ml of concentrated sulphuric acid at -10°C. Ureanitrate (2.44 g, 0.0198 mol) was added in small portions at -10°C. After the reaction the solution was poured onto ice. The solution was made alkaline and extracted with ethyl acetate. The organic extracts were dried and evaporated to dryness.

MS: 275 (21, $M^{+\cdot}$), 246 (100, M-CH_2CH_3), 200 (34, 246-NO_2), 199 (11)

Base, ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.90 (2H, q, J 7 Hz, $C\underline{H}_2CH_3$), 3.08 and 3.32 (2H, AB q, J_{AB} 16 Hz, H_2-1 or H_2-3), 3.11 and 3.38 (2H, AB q, J_{AB} 17 Hz, H_2-1 or H_2-3), 6.76 (1H, s, im-5), 7.07 (1H, d, $^3J_{HF}$ 11 Hz, H-4), 7.62 (1H, s, im-2), 7.84 (1H, d, $^4J_{HF}$ 7 Hz, H-7)

4-(5-Amino-2-ethyl-6-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

4-(2-Ethyl-5-fluoro-2,3-dihydro-6-nitro-1H-inden-2-yl)-1H-imidazole was hydrogenated to 4-(5-amino-2-ethyl-6-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole in the way described in Example 4. The yield of the crude product was 85 %. Purification was performed by flash chromatography (the eluent methylene chloride -methanol 9.5:0.5).

MS: 245 (49, $M^{+\cdot}$), 230 (12, M-CH_3), 216 (100, M-CH_2CH_3), 148 (20), 107 (18)

Base, ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.83 (2H, q, J 7 Hz, $C\underline{H}_2CH_3$), 2.90 and 3.10 (2H, AB q, J_{AB} 16 Hz, H_2-1 or H_2-3), 2.92 and 3.11 (2H, AB q, J_{AB} 15 Hz, H_2-1 or H_2-3), 6.56 (1H, d, $^4J_{HF}$ 9 Hz, H-4), 6.71 (1H, s, im-5), 6.76 (1H, d, $^3J_{HF}$ 11 Hz, H-7), 7.48 (1H, s, im-2)

4-(2-Ethyl-5,6-difluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

Fluorination of 4-(5-amino-2-ethyl-6-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was performed in the way described in Example 1.

MS: 248 (16, $M^{+\cdot}$), 219 (100, M^+.)

The hydrochloride salt, ^1H NMR (300 MHz, CD_3OD): δ 0.80 (3H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.93 (2H, q, J 7 Hz, $C\underline{H}_2CH_3$), 3.16 and 3.25 (4H, AB q, J_{AB} 16 Hz, H_2-1 and H_2-3), 7.12 (2H, dd, $^3J_{HF}$ = $^4J_{HF}$ 9 Hz, H-4 and H-7), 7.39 (1H, d, J 1 Hz, im-5), 8.87 (1H, d, J 1 Hz, im-2).

Example 10

4-(5,6-DICHLORO-2-ETHYL-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

4-(5-chloro-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole was prepared through diazotization of 4-(5-amino-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole in the way described in example 6.
The procedure of example 9 was used for the synthesis of the nitro and amino derivatives of 4-(5-chloro-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole. Chlorination was carried out as described in example 6

4-(5-chloro-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

The hydrochloride salt: Mp. 147-149°C

MS: 246/248 (28/9, M+·), 217/219 (100/33), 183 (11), 182 (16), 181 (19)

The hydrochloride salt, ^{1}H NMR (300 MHz, CD_3OD): δ 0.80 (3H, t, J 7 Hz, CH_2CH_3), 1.93 (2H, q, J 7 Hz, CH_2CH_3), 3.16 and 3.25 (2H, AB q, J_{AB}=16 Hz, the indan ring H_2-1 or H_2-3), 3.18 and 3.28 (2H, AB q, J_{AB}=16 Hz, the indan ring H_2-1 or H_2-3), 7.12-7.23 (3H, m, H-4, H-6, H-7), 7.38 (1H, d, J 1 Hz, im-5), 8.87 (1H, d, J 1 Hz, im-2)

4-(5-chloro-2-ethyl-2,3-dihydro-6-nitro-1H-inden-2-yl)-1H-imidazole

MS: 291/293 (22/7, M+.), 262/264 (100/33), 216/218 (28/9), 181 (10)

Base, ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD): δ 0.74 (3H, t, J 7 Hz, CH_2CH_3), 1.87 (2H, q, J 7 Hz, CH_2CH_3), 3.08 and 3.29 (2H, AB q, J 16 Hz, the indan ring H_2-1 or H_2-3), 3.09 and 3.32 (2H AB q, J 17 Hz, the indan ring H_2-1 or H_2-3), 6.72 (1H, s, im-5), 7.34 (1H, s, H-4), 7.56 (1H, s, im-2), 7.69 (1H, s, H-7)

4-(5-amino-6-chloro-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

MS: 261/263 (60/24, M+·), 232/234 (100/35), 196 (53)

Base, ^{1}H NMR: (300 MHz, CD_3OD): δ 0.71 (3 H, t, J 7 Hz, CH_2CH_3), 1.81 (2H, q, J 7 Hz, CH_2CH_3), 2.91 and 3.10 (4H, AB q, J 15 Hz the indan ring H_2-1 and H_2-3), 6.68 (1H, s, H-4), 6.76 (1H, d, J 1 Hz, im-5), 6.99 (1H, s, H-7), 7.61 (1 H, J 1 Hz, im-2)

4-(5,6-dichloro-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole

MS: 280/282/284 (22/14/2, M+.), 251/253/255 (100/64/11)

Base, ^{1}H NMR (300 MHz, CD_3OD): δ 0.72 (3 H, t, J 7 Hz, CH_2CH_3), 1.84 (q, 2H, J 7 Hz, CH_2CH_3), 2.99 and 3.21 (4H, AB, q, J 16 Hz, the indan ring H_2-1 and H_2-3) , 6.80 (1H, s, im-5), 7.26 (2H, s, ArH), 7.61 (1H, s, im-2)

Example 11

4-(5-CHLORO-2-ETHYL-6-FLUORO-2,3-DIHYDRO-1H-INDEN-2-YL)-1H-IMIDAZOLE

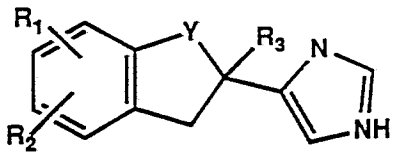
Chlorination of 4-(5-amino-2-ethyl-6-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole (cf example 9) was carried out as described in example 6.

MS: 264/266 (34/11, M+.) 235/237 (100/35)

Base, ^{1}H NMR (300 MHz, CD_3OD): δ 0.72 (3H, t, J 7 Hz, CH_2CH_3), 1.85 (2H, q, J 7 Hz, CH_2CH_3), 3.00 and 3.20 (2H, AB q, J 16 Hz, the indan ring H_2-1 or H_2-3), 3.02 and 3.22 (2H, AB q, J 16 Hz, the indan ring H_2-1 or H_2-3), 6.80 (1H, s, im-5), 7.02 (1H, d, $^3J_{HF}$ 9 Hz, H-4), 7.22 (1H, d, $^4J_{HF}$ 7 Hz, H-7), 7.62 (1H, s, im-2)

CLAIMS

1. Substituted imidazoles according to the general formula



(I)

wherein
Y is $-CH_2-$ or -CO-
R_1 is F, Cl or OH; R_2 is H, F or Cl; and R_3 is H, CH_3 or CH_2CH_3, excluding 4-(5-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(4-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 where R_1 is F and R_2 is H or F.

3. A compound according to claim 2 where R_2 is H.

4. A compound according to claim 1, wherein R_3 is hydrogen or CH_2CH_3.

5. A compound according to claim 1, wherein Y is $-CH_2-$.

6. 4-(2-Ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole or its pharmaceutically acceptable non-toxic salt.

7. 4-(5-Fluoro-2,3-dihydro-2-methyl-1H-inden-2-yl)-1H-imidazole or its pharmaceutically acceptable non-toxic salt.

8. 4-(2-Ethyl-5,6-difluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole or its pharmaceutically acceptable non-toxic salt.

9. 2-Ethyl-6-fluoro-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one or its pharmaceutically acceptable non-toxic salt.

10. 6-Chloro-2-ethyl-2,3-dihydro-2-(1H-imidazol-4-yl)-1H-inden-1-one or its pharmaceutically acceptable non-toxic salt.

11. 4-(4-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole or its pharmaceutically acceptable non-toxic salt.

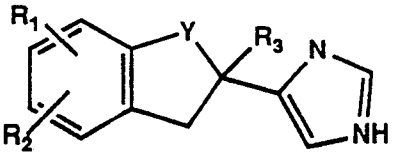
12. 4-(5-Fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole or its pharmaceutically acceptable non-toxic salt.

13. 2-Ethyl-2-(1H-imidazol-4-yl)-5-indanol or its pharmaceutically acceptable non-toxic salt.

14. 4-(5,6-dichloro-2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole or its pharmaceutically acceptable non-toxic salt.

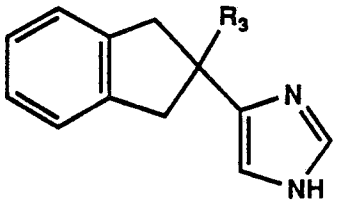
15. 4-(5-chloro-2-ethyl-2,3-dihydro-6-nitro-1H-inden-2-yl)-1H-imidazole or its pharmaceutically acceptable non-toxic salt.

16. A method for the preparation of the compound according to the general formula I



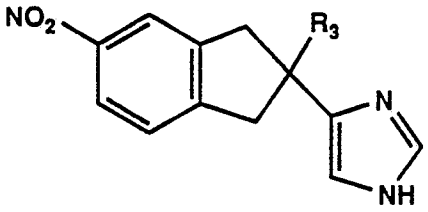
(I)

wherein
Y is $-CH_2-$
R_1 is F or Cl; R_2 is H and R_3 is H, CH_3 or CH_2CH_3
c h a r a c t e r i z e d in that a compound of formula (II)

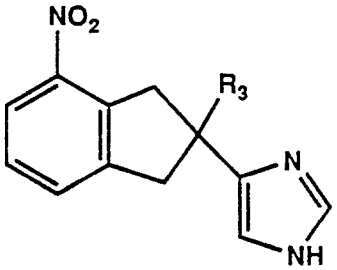


(II)

where R_3 is as defined above is nitrated to give the compounds of formulae (III) and (IV)

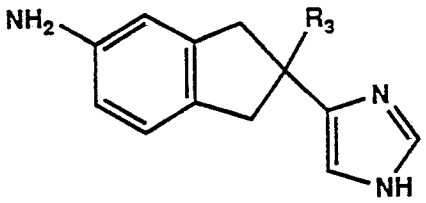


(III)

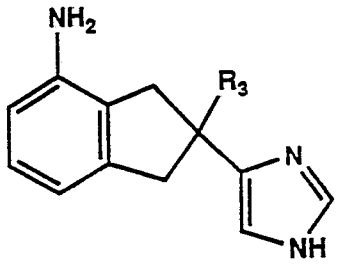


(IV)

which are optionally separated from each other and further reduced to the corresponding amino substituted compounds of formulae (V) and (VI)

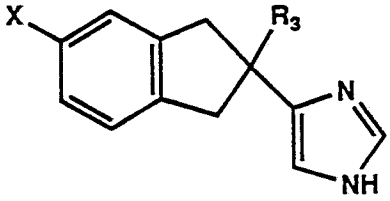


(V)

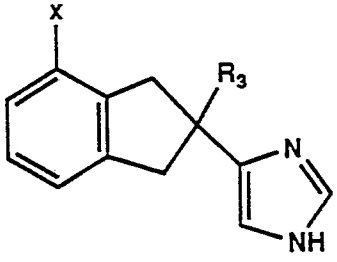


(VI)

which are optionally separated from each other and are converted to their corresponding diazonium salts whereafter the diazonium groups are replaced with the corresponding halogen to yield the compounds of formulae (VII) and (VIII)



(VII)



(VIII)

where X is F or Cl.

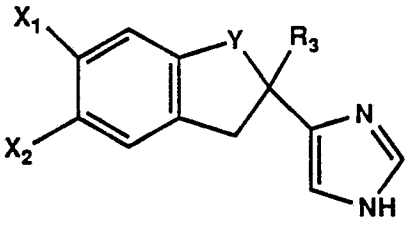
17. A method according to claim 16, characterized in that in the formulae VII and VIII X is F.

18. A method according to claim 17, c h a r a c t e r i z e d in that the said diazonium salts are generated by reacting the amine of formula V and/or VI with mineralic acid on sodium nitrite at lowered temperature.

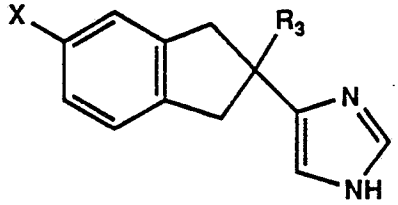
19. A method according to claim 16 , c h a r a c t e r i z e d in that in the formulae VII and VIII X is Cl.

20. A method according to claim 19 , c h a r a c t e r i z e d in that the said diazonium salts are formed by reacting the amine of formula V and/or VI with hydrochloric acid and sodium nitrite at lowered temperature.

21. A method for the preparation of the compound according to the general formula

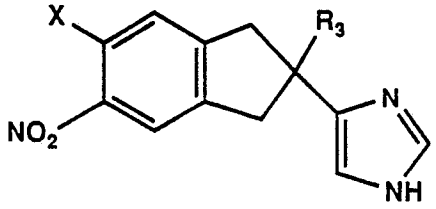


wherein
Y is $-CH_2-$
X_1 is F or Cl;
X_2 is F or Cl and R_3 is H, CH_3 or CH_2CH_3
c h a r a c t e r i z e d in that a compound of formula VII



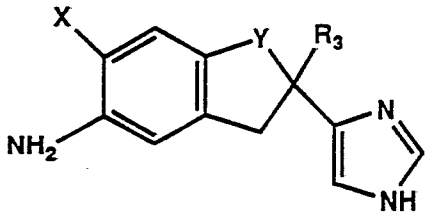
(VII)

wherein X is F or Cl and R_3 is the same as defined above is nitrated to give a compound of formula IX



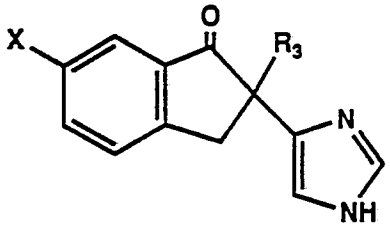
(IX)

and the nitro group is further reduced to the corresponding amino group

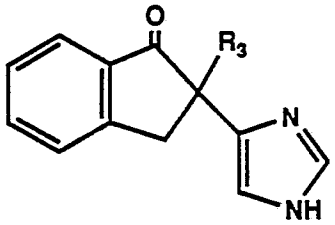


wherafter the amino group is converted to the corresponding diazonium group which is converted to the corresponding halogen.

22. A method for the preparation of the compound according to general formula X

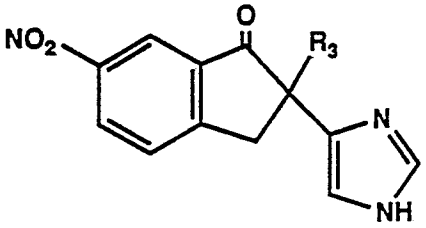


wherein
X is F or Cl and R_3 is H, CH_3 or CH_2CH_3
c h a r a c t e r i z e d in that a compound of formula XI

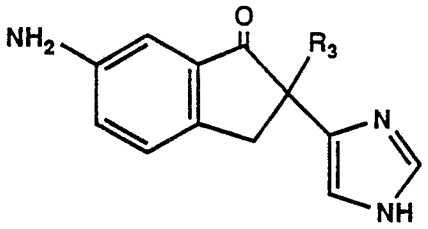


(XI)

where R_3 is the same as defined above is nitrated

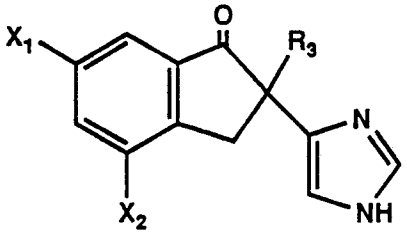


and the nitro group is reduced to the corresponding amino group

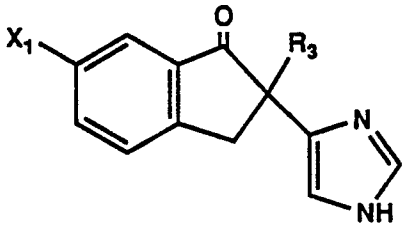


which further is converted to a diazonium group which is thereafter converted to the corresponding halogen.

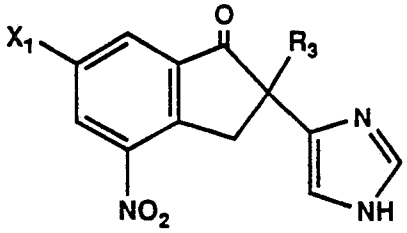
23. A method for the preparation of the compound according to general formula



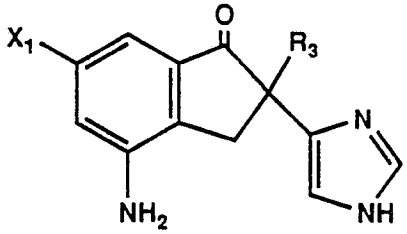
X_1 is F or Cl, X_2 is F or Cl and R_3 is H, CH_3 or CH_2CH_3 characterized in that a compound of formula



wherein X_1 and R_3 are the same as defined above is nitrated to give the compound of formula

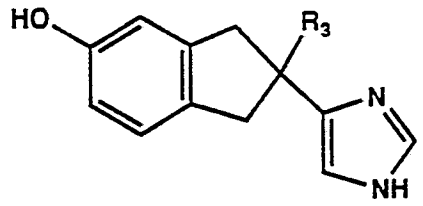


and the nitro group is reduced to an amino group



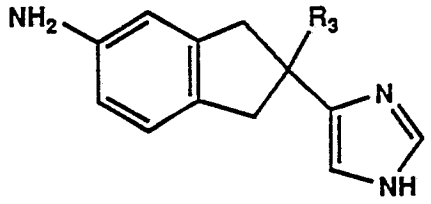
whereafter the amino group is converted to the corresponding diazonium group and the diazonium group is converted to the corresponding halogen.

24. A method for the preparation of a compound according to the general formula XII



(XII)

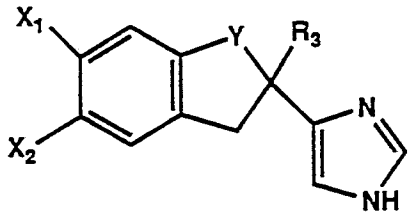
where R_3 is H, CH_3 or CH_2CH_3 characterized in that a compound of the general formula V



(V)

where R_3 is the same as given above is reacted with sodium nitrite in the presence of concentrated sulfuric acid at lowered temperature and the diazonium salt thus obtained is decomposed to yield the compound of formula (XII).

25. A new intermediate according to the general formula



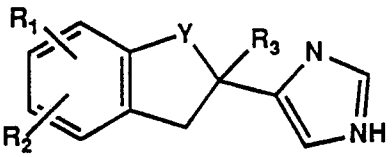
wherein

Y is $-CH_2-$ or -CO-

X_1 is F or Cl;

X_2 is F or Cl and R_3 is H, CH_3 or CH_2CH_3 excluding 4-(5-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(4-chloro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole.

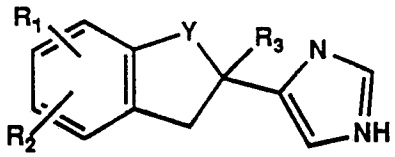
26. An oral composition comprising a substituted imidazole according to the general formula



(I)

wherein
Y is $-CH_2-$ or -CO-
R_1 is F, Cl or OH; R_2 is H, F or Cl; and R_3 is H or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

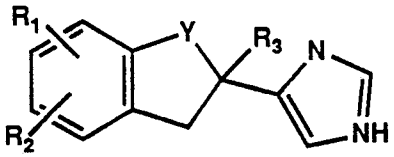
27.Use of a substituted imidazole according to the general formula



(I)

wherein
Y is $-CH_2-$ or -CO-
R_1 is F, Cl or OH; R_2 is H, F or Cl; and R_3 is H and pharmaceutically acceptable salts thereof for the manufacture of a medicament for use in the treatment of cognitive disorders.

28. A method of treatment of cognitive disorders comprising administering to a subject an effective amount of a substituted imidazole according to the general formula



(I)

wherein
Y is $-CH_2-$ or -CO-
R_1 is F, Cl or OH; R_2 is H, F or Cl; and R_3 is H or a pharmaceutically acceptable salts thereof.

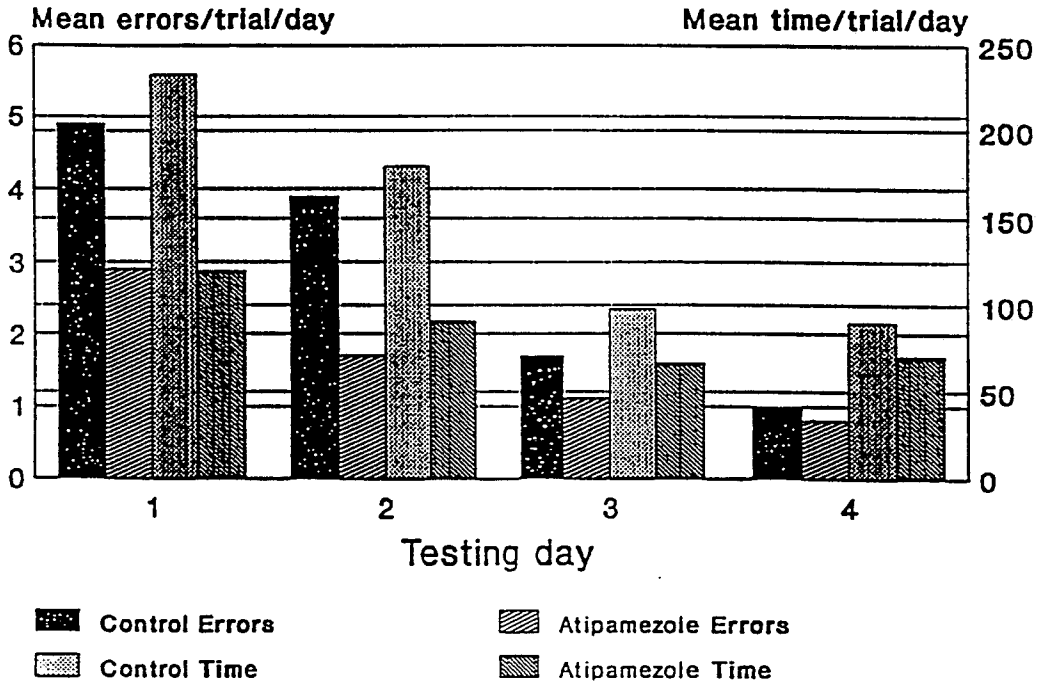

Mean errors/trial/day
Mean time/trial/day
6
5
4
3
2
1
0
250
200
150
100
50
0
1
2
3
4
Testing day
Control Errors
Control Time
Atipamezole Errors
Atipamezole Time

FIG 1

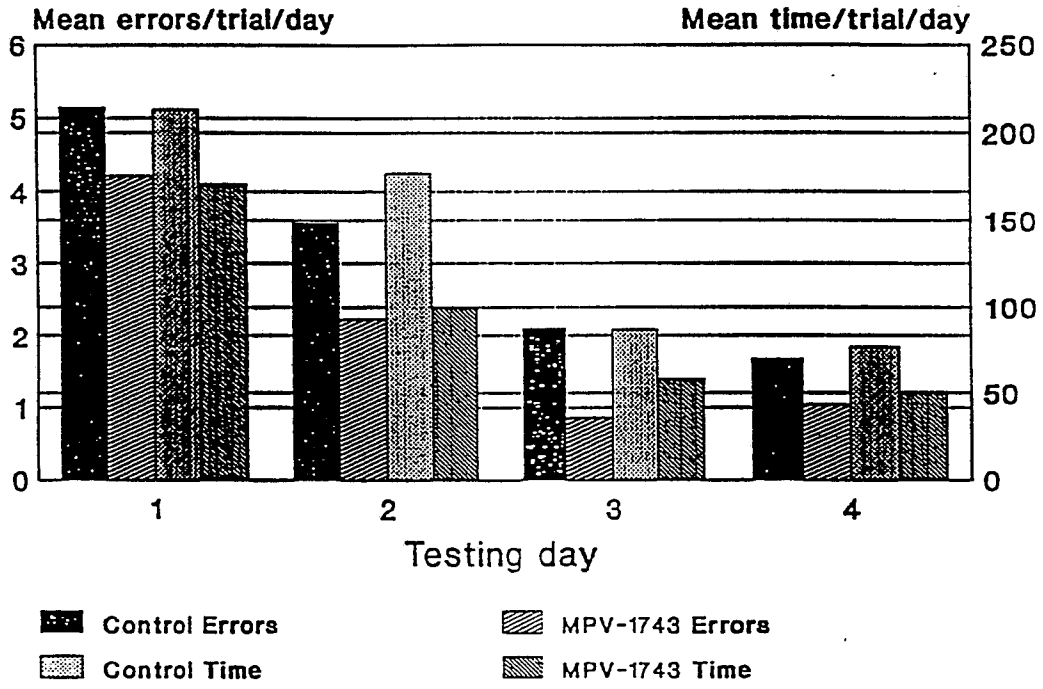

Mean errors/trial/day
Mean time/trial/day
6
5
4
3
2
1
0
250
200
150
100
50
0
1
2
3
4
Testing day
Control Errors
Control Time
MPV-1743 Errors
MPV-1743 Time

FIG 2

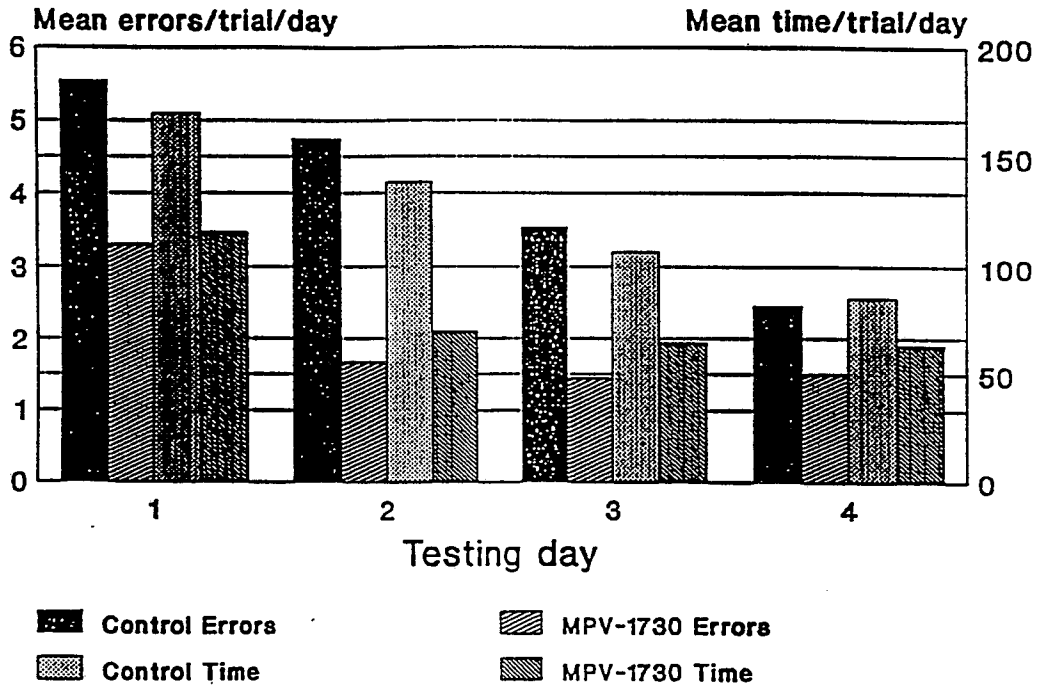

Mean errors/trial/day
Mean time/trial/day
6
5
4
3
2
1
0
200
150
100
50
0
1
2
3
4
Testing day
Control Errors
Control Time
MPV-1730 Errors
MPV-1730 Time

FIG 3

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D233/54; A61K31/415

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 310 745 (FARMOS-YHTYMA OY) 12 April 1989 see claims	1,16, 25-27
A	EP,A,0 372 954 (FARMOS-YHTYMA OY) 13 June 1990 cited in the application see the whole document	1,16, 25-27

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30 MARCH 1993	14. 04. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FRANCOIS J.C.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claim 28 is directed to a method of the treatment of the human body, the search has been carried out and based on the alleged effects of the compounds."

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

FI 9200349
SA 68775

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 30/03/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0310745	12-04-89	GB-A- 2167408	29-05-86
		AU-A- 3332989	10-08-89
		AU-B- 586839	27-07-89
		AU-A- 5008385	29-05-86
		CA-A,C 1266669	13-03-90
		EP-A,B 0183492	04-06-86
		JP-A- 61143366	01-07-86
		SU-A- 1424736	15-09-88
		US-A- 4689339	25-08-87
EP-A-0372954	13-06-90	GB-A- 2225782	13-06-90
		AU-B- 619928	06-02-92
		AU-A- 4599289	16-08-90
		JP-A- 2202874	10-08-90